

Application No. 10/609,346  
Response Dated April 11, 2007  
Reply to Office Action of December 19, 2006

### **REMARKS/ARGUMENTS**

#### **1. Remarks on the Information Disclosure Statement**

Applicants submitted an Information Disclosure Statement on March 18, 2007, together with a fee in amount of \$180 in accordance with 37 C.F.R. 1.97(c)(2) and 1.17(p). Applicants respectfully request the Examiner's consideration of the references submitted.

#### **2. Response to the Rejection of Claims 51 under 35 U.S.C. §112, first paragraph**

Claim 51 stands rejected under 35 USC §112, first paragraph. This rejection is respectfully traversed.

Applicants submit herein a Statement on Deposit of Biological Material Pursuant To 37 CFR 1.808, which states that deposit of the biological materials described in the instant application has been made under the terms of the Budapest Treaty, and all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

Therefore, Applicants submit that Claim 51 satisfies the requirement of 35 USC §112, first paragraph.

Accordingly, Applicants respectfully request withdrawal of the rejection based upon 35 U.S.C. §112, first paragraph.

#### **3. Response to the Rejection of Claims 51-67 under under 35 U.S.C. §112, second paragraph**

Claims 51-67 stand rejected under 35 USC §112, second paragraph. This rejection is respectfully traversed by the amendment.

The Specification and Claims 51-53 and 61-67 have been amended to comply with 35 U.S.C. §112, second paragraph. Applicants submit that no new matter has been introduced by the amendment.

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Accordingly, Applicants respectfully request withdrawal of the rejection based upon 35 U.S.C. §112, second paragraph.

4. Response to the Rejection of Claims 51-67 under under 35 U.S.C. §103(a)

Claims 51-67 stand rejected under 35 USC §103(a) as being unpatentable over Shaw (U.S. Patent No. 4,904,584) in view of the Capon et al. (U.S. Patent No. 5,116,964). This rejection is respectfully traversed.

Applicants submit that nothing in the art of record teaches or suggests the subject matter positively recited in the Claim 51. As recited in Claim 51, Applicants' claimed recombinant polynucleotide that comprises a member selected from the group consisting of (a) a polynucleotide encoding a polypeptide as set forth in SEQ ID NO. 8; and (b) a polynucleotide contained in ATCC<sup>®</sup> Deposit No: PTA-4607.

The Examiner states that Shaw has only been relied upon for the disclosure of the method of producing recombinant G-CSF using the DNA encoding G-CSF. As pointed out by the Examiner, Shaw fails to teach a polynucleotide encoding both G-CSF and albumin to obtain a fusion protein comprising G-CSF and albumin to increase the half-life of G-CSF.

Shaw's deficiencies are not overcome by Capon et al. Capon et al. fail to teach Applicant's claimed polynucleotide encoding a polypeptide as set forth in SEQ ID NO. 8, or a polynucleotide contained in ATCC<sup>®</sup> Deposit No: PTA-4607, which encodes a HSA/G-CSF fusion protein.

In reviewing the final Office Action, Applicants strongly disagree with the Examiner's construction of Capon et al's teaching. In view of the Examiner's understanding of the prior art of record and the state of art at the time that the present invention was made, Applicants respectfully provide the following remarks.

1. The Examiner states that the teaching of Capon could be taken by any skilled artisan to encompass "any" soluble protein. Applicants respectfully point out that this statement is an improper construction of the actual teaching of the reference.

Applicants summarize Capon et al' teaching below:

(1) Capon et al. teach nucleic acid encoding a polypeptide fusion comprising a

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ligand binding partner protein fused to a stable plasma protein. The ligand binding partner is proteins known to function to bind specifically to target ligand molecules.

(2) Capon et al. teach that the stable plasma protein extends the in vivo plasma half-life of the ligand binding partner when present as a fusion with the ligand binding partner.

(3) Capon et al. specifically teach that a large number of proteins having various structures, sources, and biological functions are excluded from the ligand binding partner, and therefore, not suitable for their invention. More specifically, Applicants recites below Capon's teaching:

As used herein, the term "ligand binding partner" specifically excludes polymorphic and nonpolymorphic members of the immunoglobulin gene superfamily, and proteins which are homologous thereto, such as class I and class II major histocompatibility antigens, immunoglobulins, T-cell receptor  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  chains, CD1, CD2, CD4, CD8, CD28, the  $\gamma$ ,  $\delta$  and  $\epsilon$  chains of CD3, OX-2, Thy-1, the intercellular or neural cell adhesion molecules (I-CAM or N-CAM), lymphocyte function associated antigen.3 (LFA.3), neurocytoplasmic protein (NCP-3) poly-Ig receptor myelin-associated glycoprotein (MAG), high affinity IgE receptor, the major glycoprotein of peripheral myelin (Po), platelet derived growth factor receptor, colony stimulating factor.1 receptor, macrophage Fc receptor, Fc gamma receptors and carcinoembryonic antigen (Column 7, lines 35-50, of the reference).

This list excludes more than 20 named proteins and families. Colony stimulating factor 1 receptor is one of these excluded proteins, which is related to G-CSF as discussed in detail in the previous response dated November 21, 2006.

In the section of the reference that the Examiner recited in the Office Action, Capon et al teach "the objects of this invention are accomplished by providing novel polypeptides comprising a ligand binding partner fused to a stable plasma protein". As discussed above, the "ligand binding partner", as defined by Capon, excludes many

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proteins, more particularly, colony stimulating factor 1 receptor.

Therefore, the Examiner's construction that Capon provides the express motivation to add the albumin to any soluble protein to increase its circulating half-life is not consistent with the express teaching of Capon et al.

2. The Examiner states that if Capon et al disclosed the instant HSA/G-CSF fusion protein, the rejection would be under 35 USC 102(b), rather than under 35 USC 103(a).

Applicants respectfully point out that Applicants' entire arguments presented in the previous response are based on 35 USC 103(a).

More specifically, *In re Dow Chem.*, 837 F.2d 469, 473, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988) clearly states that "the consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art."

Applicants maintain that because of Capon et al's specific exclusions of the proteins closely related to G-CSF of the instant invention, Capon et al teach away from Applicants' claimed invention. As such, it is improper to consider that Capon et al's teaching is the genus, and the instant invention is merely a species of this genus.

The Examiner further states in the Advisory Action that the instant claims are drawn to G-CSF not the G-CSF receptor; ligand and their receptors are very disparate, structurally, materially and functionally, and therefore, Capon et al fail to exclude the G-CSF and albumin fusion protein.

Based on this rationale, however, Applicants have to point out that Capon et al merely teach the fusion of receptor proteins, not the proteins that function as a ligand, i.e., G-CSF protein (with respect to G-CSF receptor). Furthermore, Applicants respectfully point out that the Examiner's positions are contradictory. On one hand, the Examiner considers that Capon et al's teaching encompasses all soluble proteins, regardless their structures and functions. On the other hand, the Examiner considers that ligand and their receptors are very disparate, structurally, materially and functionally, therefore, Capon et al only excludes CSF-1 receptor, but not CSF-1 protein or its closed

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related G-CSF protein. It is apparent that the Examiner's constructions of the scope of Capon et al's teaching are contradictory on its own.

3. The Examiner states that vast majority of generic proteins in Class 435 are predicted on the presumption that one can reasonably fuse a first protein to a second protein and expect success. The Examiner further rationalizes that the reason is the vast majority of proteins not requiring a free amino or carboxy group for activity.

Applicants respectfully point out that this is an oversimplification of the daunting tasks that the biopharmaceutical industry is facing. Today, the industry spends millions of dollars every year and hires thousands of Ph.D.s to discover and develop bioactive fusion proteins which are suitable for pharmaceutical use. One of the major difficulties is that after fusion the protein properties can change, which can attribute to many reasons, such as primary, secondary or tertiary structure changes, steric hindrance, interference to binding to the receptors, and etc. Any of these reasons can substantially affect the bioactivity of the fusion proteins. Various scientific publications have reported loss of protein activity, or substantial reduction of the activity after fusion, which diminishes the utility of the fusion proteins.

Applicants provide below a few research reports that illustrate the practical issues regarding the fusion proteins and specific findings with regard to G-CSF fusion protein, which clearly set the foundation that shows the unexpected results of the rHAS/G-CSF fusion protein encoded by the instant recombinant polynucleotide, as further discussed hereinafter.

It is noted that all references discussed herein were enclosed in the IDS submitted on March 18, 2007.

First, in general, it is well known that in fusion proteins a peptide linker or spacer is used between two domains to preserve the functions of the individual domains. Argos and Robinson et al have reported that the flexibility and hydrophilicity of the peptide linkers are important for preservation of the functions of the individual domains in a fusion protein (Argos, *J. Mol. Biol.* 211:943-958, 1990 and Robinson et al, *Proc. Natl. Acad. Sci. USA* 95:5929-5934, 1998).

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However, Maeda et al have reported that some fusion proteins may lose their activity using the flexible spacer to link the two moieties (Maeda et al, *Anal. Biochem.* 249:147-152, 1997).

From these references, it is apparent that the presence and proper selection of a spacer between the two functional domains can be critical to the property and the activity of the resultant fusion protein.

Second, with regard to G-CSF, through extensive research of functional domain of human G-CSF, Layton et al have reported that residues 20-46 at the N-terminal and the COOH terminus of G-CSF are involved in binding to G-CSF receptor (Layton et al, *The Journal of Biological Chemistry*, vol. 266, No. 35, Issue of December 15, pp. 23915-23823, 1991).

Based on Layton et al's teaching, fusion at either C-terminal or at N-terminal could affect biological activity of the G-CSF domain in the fusion protein, because in the former C-terminus will be blocked; and in the latter residues 20-46 are very close to N-terminus and fusion to another protein at N-terminus could change conformation of adjacent regions.

Third, a practical example of this concern has been reported in Bai et al's most recent research of G-CSF and transferrin fusion protein (Bai et al, *Pharmaceutical Research*, Vol. 23, No. 9, September 2006).

In the study of improving the oral efficiency of recombinant G-CSF-Tf fusion protein, Bai et al have found that the G-CSF-Tf fusion protein only retained a small fraction of the in vitro activity of both cell proliferation of G-CSF and TfR-binding of Tf. Bai et al attribute the activity loss of Tf to the modification of the N-terminus of Tf domain rather than a steric hindrance of the receptor binding site in the fusion protein, based on analysis of multiple G-CSF-Tf fusion proteins having different linkers.

More importantly, in the attempt of reversing the sequence of G-CSF and Tf in the fusion protein, the fusion protein produced from Tf-G-CSF expression was inactive, when evaluating the activity of G-CSF by NFS-60 cell proliferation assay (see page 2120, Column 2, the first paragraph, of the reference).

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Based on the above, it is apparent that either at the time of the present invention was made, or today, without undue experimentations to actually express a specific fusion protein and testing its property and bio-activity in vitro and in vivo, one of ordinary skill in the art would not be able to predict whether a fusion protein retains the desired biological functions and a reasonable amount of bio-activity that merits its utility.

In the instant situation, Capon et al fail to teach any specifics on how to fuse albumin to G-SCF, such as through C- or N-terminal of G-CSF, using or not using linkers, what type of linkers, and how to preserve bioactivity of G-CSF.

Fourth, Applicants point out that it is important to understand that the fusion protein encoded by the instant recombinant polynucleotide, as defined in Claim 51, is a directly fused protein that does not have any peptide linker between the two domains.

Unexpectedly, the present inventors have discovered that the rHAS/G-CSF fusion protein encoded by the instant recombinant polynucleotide does not require a peptide linker, and the retained bioactivity of the directly fused protein warrants its utility. This unexpected result is substantially different from the teachings of the existing art, as illustrated above.

Therefore, Applicants maintain that Applicants' claimed invention as defined by Claim 51 is not obvious in view of the prior art of record.

With regard to Claims 52-67, these claims are dependent claims of independent Claim 51. Under the principles of 35 U.S.C. §112, 4<sup>th</sup> paragraph, all of the limitations of each independent claim are recited in its respective dependent claims. As described above, independent Claim 51 is unobvious in view of the prior art of record, as such Claims 52-67 are submitted as being allowable over the art of record.

Accordingly, Applicants respectfully request withdrawal of the rejection based upon 35 U.S.C. §103(a).

It is respectfully submitted that Claims 51-67, the pending claims, are now in condition for allowance and such action is respectfully requested.

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Applicants' Agent respectfully requests direct telephone communication from the Examiner with a view toward any further action deemed necessary to place the application in final condition for allowance.

4/11/2007  
Date of Signature

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